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# Resilience of the oral microbiome

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## 1 | INTRODUCTION

The term resilience was first used in an ecological sense by Holling,[1] who defined it as the ability of a system to resist change and persist, in contrast to stability, which was defined as the ability of a system to return to a state of equilibrium after a temporary disturbance. A system may therefore have high resilience because it persists, but low stability because its populations show a high degree of fluctuation. Low stability may, in fact, lend resilience to a system as a way of absorbing external influences. These concepts are highly relevant to the oral microbiome, which is subject to external influences from the host and the environment as a result of the host's behavior. Resilience should not be confused with health. A microbial community may achieve a resilient state as a result of the influence of external factors on the original system. Thus, an individual with poor oral hygiene will accumulate a mature biofilm on oral surfaces, which will lead to gingivitis. This disease-associated community will exhibit resilience and be difficult to return to a microbiota associated with health, particularly without disruption of the biofilm by mechanical treatment methods.

In addition, resilience can be observed at the level of the individual as well as the microbiota. It has often been observed that individuals vary in their susceptibility to dental plaque-related diseases when exposed to similar environmental factors. Not all individuals experience dental caries to the same degree when exposed to a high level of fermentable carbohydrate,[2] and it has been shown experimentally that the levels of gingivitis can vary considerably when oral hygiene is withdrawn.[3] Host factors, such as salivary and serum antibody levels and elements of innate immunity, are thought to be responsible for these differences, as recently reviewed by Rosier et al.[4]

This review will focus on the resilience of oral microorganisms themselves, both individually and particularly when organized as communities. The interaction of the microbiome with external factors will be discussed, and the underlying principles which determine the outcome in terms of bacterial community composition and function will be explored. An overview of the factors involved and the outcomes that they influence is shown in Figure 1. The resilience of resident oral archaeal, viral, fungal, and protozoal communities has rarely been addressed to date and is a major future research goal. For that reason, except where stated, this review will focus on oral bacterial communities.

## 2 | COMPOSITION OF THE ORAL MICROBIOME

The composition of the oral microbiome has been reviewed previously.[5] Representatives of the Bacteria, Archaea, fungi, protozoa and viruses are present. Recent studies have revealed major new branches of the Bacteria and Archaea. The Candidate Phyla Radiation group within the domain Bacteria may make up to half of bacterial life on earth and members of this group appear to be ubiquitous.[6,7] Interestingly, the organisms within this group studied thus far are small in size, typically passing through filters with a pore-size diameter of 0.2 μm, and have small genomes which lack some genes encoding essential functions.[8] This makes them dependent on other bacteria for growth, either growing closely together in an epibiotic way or demonstrating frank parasitism by invading the cells of other bacteria.[9] Three Candidate Phyla Radiation candidate phyla are found in the mouth: Candidatus Saccharibacteria (originally described as Candidate Division TM7), Candidatus Absconditabacteria (SR1), and Candidatus Gracilibacteria (GN02). Representatives of Saccharibacteria have been cultivated in association with *Actinomyces* species.[9,10] An analogous group, the DPANN

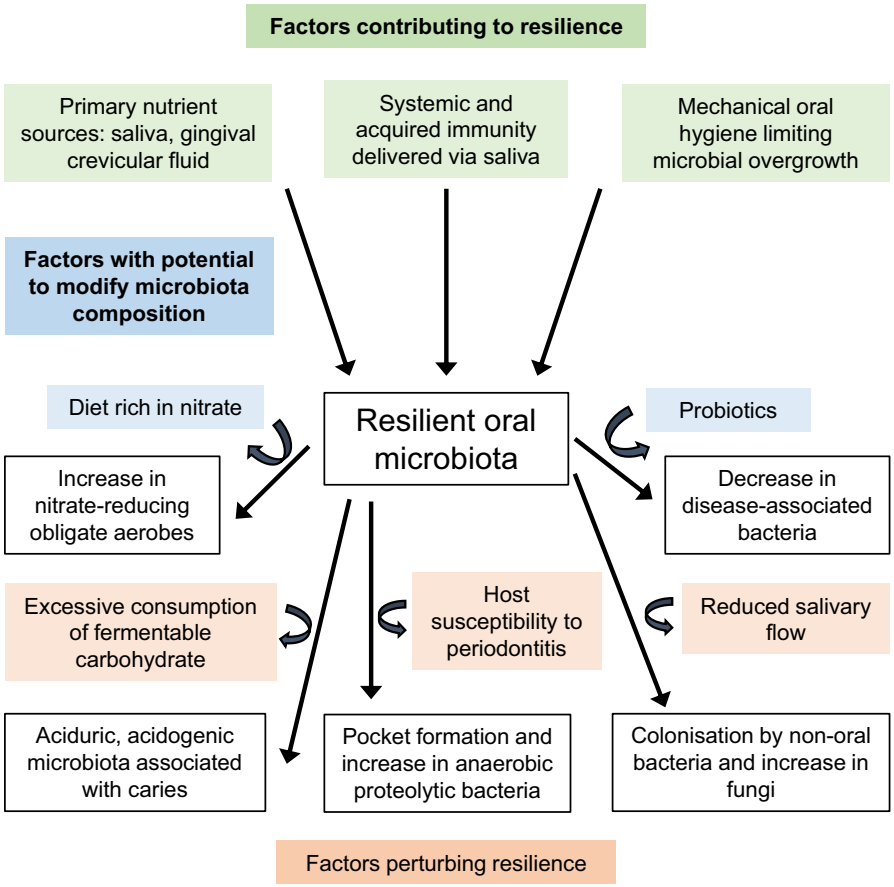


**FIGURE 1** Overview of factors influencing the composition and resilience of the oral microbiota

superphylum, has been found within the Archaea.[11] The viruses of the human gut have also been explored in detail, particularly the extensive population of phage that are found to infect oral bacteria, and which undoubtedly contribute to their properties, and perhaps also to their virulence.[12]

Community profiling studies have found around 300 species of bacteria in a single person at any one time and have revealed that those species, and their proportions, are remarkably stable over time,[13,14] to the point where there may be potential for forensic use in identifying individuals.[15] There is considerable overlap in the functional potential of oral bacterial species and it has been shown that although the taxonomic composition of the oral microbiota differs between individuals, there are broad functional similarities among the bacterial communities of individuals.[16]

## 3 | NUTRITION AND EFFECT OF DIET

It is often assumed that because the mouth is the portal of entry for food into the body, the human diet must influence the composition of the oral microbiome. As eating is accompanied by chewing and stimulation of salivary flow, food is actually present in the mouth for only limited periods during the day and it has been shown that the primary nutritional sources for oral bacteria are saliva and gingival crevicular fluid.[17] Oral bacteria work as a consortium to break down and utilize these substrates. Streptococci, in particular, play a primary role in obtaining sugar residues from glycoproteins. For example, *Streptococcus oralis*, when grown on acute phase serum alpha 1-acid glycoprotein, produced a range of glycosidases, including sialidase, *N*-acetyl-beta-D-glucosaminidase, and beta-D-galactosidase, which led to extensive degradation of all glycan chains with only terminal *N*-acetylglucosamine residues remaining when growth was complete (Byers et al.[115]). Monosaccharides were released sequentially from glycans in the order: sialic acid, galactose, fucose, nonterminal *N*-acetylglucosamine, and mannose. All monosaccharides were metabolized by *S oralis*, except for fucose. Subsequently, protein backbones are degraded by proteolytic gram-negative anaerobes, such as *Porphyromonas* and *Prevotella* species,[18,19] and then amino acids are released from peptides by organisms with aminopeptidase activity, such as *Parvimonas micra*, and fermented by common oral bacteria, including *Fusobacterium nucleatum*.[17,20]

In short-term studies in animal models, no differences in growth rates of oral bacteria were seen in the presence or absence of food,[21] and no differences in the total numbers of bacteria in saliva were seen in animals after 18 h of fasting compared with fed animals.[22] The majority of human studies have found no relationship between diet and the composition of oral bacterial communities. A study of 161 subjects revealed a large core microbiota in more than 98% of the subjects and no differences when the subjects were grouped according to their diet (omnivorous, ovo-lacto-vegetarian, or vegan).[23] Interestingly, differences were found in the salivary metabolomic profiles between the 3 dietary groups, suggesting that circulating

metabolites originating from the large intestine were detectable in saliva. The subjects could also be grouped into 3 salivary types on the basis of proportions of the core genera *Prevotella*, *Streptococcus*, *Gemella*, *Fusobacterium*, and *Neisseria*. A similar finding was seen in a "citizen science" study of 1500 adolescents in Spain, who were found to belong to 1 of 2 stomatotypes defined by the relative abundance of *Neisseria* and *Prevotella*, respectively, and which the authors considered were fundamental microbiome assemblies reflecting the human oral ecosystem and which they predicted would be replicated in humans at all geographic locations.[24] This intriguing finding deserves further study. Characterization of the oral microbiome of Batwa pygmies found 40 bacterial genera, not previously reported in humans, in their saliva.[25] Many of these genera, however, are well-known reagent contaminants.[26] It therefore remains to be confirmed whether these genera were true residents of the subjects' mouths in this population.

There were no overall differences in composition of the bacterial community in saliva from athletes on low-, periodic-, and high-carbohydrate diets for 3 weeks, although comparison of specific taxa at the end of the study period with those at baseline found, perhaps surprisingly, that proportions of the genus *Streptococcus* were increased in athletes on the low-carbohydrate diet.[27] Samples collected from 6 oral sites in volunteers who consumed a high-sucrose diet for 21 days showed changes in composition of the bacterial community, albeit of low magnitude and with high variability between subjects.[28]

A small-scale study of 24 subjects found differences in the bacterial composition of salivary rinse samples collected from hunter-gatherers and traditional farmers in the Phillipines when compared with publicly available data from the Human Microbiome Project.[29] The hunter-gatherers had higher levels of species previously associated with periodontitis, such as *Prevotella intermedia*, *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans*, and *Eubacterium nodatum* than the traditional farmers, although their oral health was reportedly better. A major weakness of this study was that oral health indices were not formally measured. It is highly likely that there were differences in oral hygiene practice and consequent overall plaque maturity between the groups, which explain the differences seen. Moreover, periodontitis is notoriously difficult to diagnose without detailed periodontal examination.

## 4 | EFFECT OF ANTIMICROBIAL TREATMENT: ORAL HYGIENE

Arguably the single most important external factor affecting the contemporary oral microbiome is the practice of oral hygiene, the result of which is that dental plaque is maintained in an immature state with high proportions of early plaque-forming bacteria, particularly streptococci. Evidence for this has been found in the plaque deposits preserved in calculus in archaeological specimens. These plaques have a far higher proportion of anaerobes than contemporary plaque because the maturation of plaque has been interrupted by oral hygiene in the latter.[30]

Standard toothpastes contain abrasives and detergents to help remove plaque, and flavoring is added. Most toothpastes also include fluoride,[31] primarily because fluoride interacts with hydroxyapatite in enamel to form fluorapatite, which makes the enamel more resistant to demineralization by acid. In addition, fluoride has antibacterial properties in that it can directly reduce acid production by saccharolytic bacteria through inhibiting enolase (part of the tricarboxylic acid cycle), increase cell-membrane permeability (thereby reducing acid tolerance), and form metal-fluoride complexes that inhibit enzyme activity.[32] Whether fluoride has an effect on the composition of the oral microbiome is unclear because its use is so widespread that it is not possible to include meaningful control groups in studies. In an in-vitro biofilm model, however, fluoride treatment had no effect on bacterial numbers, but acid production was reduced.[33]

Brushing with toothpaste may not provide optimal plaque removal, and a variety of chemical agents have been added to dentifrices and other delivery vehicles in an attempt to control plaque more effectively. Such agents include chlorhexidine, cetyl pyridinium chloride, triclosan, zinc citrate, delmopinol, amine and stannous fluorides, and essential oils, and evidence is available to suggest some clinical benefit of their use (reviewed by Serrano et al[34]). In addition, detergents in toothpastes contribute antimicrobial properties to formulations which may be as substantial of those of the active ingredients themselves. For example, sodium lauryl sulfate and triclosan, at concentrations at which they are commonly included in oral care products, displayed approximately similar activities against a panel of oral bacteria.[35]

Many of these active agents are extremely potent in laboratory evaluations but typically show far more limited activity in vivo. There are a number of reasons for this. Salivary flow means that agents need to be able to be retained in the mouth and this is achieved typically by the agents becoming bound to oral surfaces. Often, however, this binding inactivates the agents. Retention of anti-plaque activity when bound is known as substantivity.[36] A major reason why active ingredients and formulations of oral care products are ineffective in vivo is that oral bacteria are naturally found in the mouth as biofilms. It has long been known that bacteria growing as biofilms are orders of magnitude more resistant to antimicrobials than planktonic cells. This has been shown to be physical, through preventing diffusion of the agent into the biofilm, particularly for agents that are charged and interact with the biofilm surface, and because of the altered phenotype that cells adopt when grown in a biofilm.[37] For example, it has been shown that, after exposure to chlorhexidine, mixed oral bacteria are killed more than 13 times more slowly when in a biofilm than in planktonic growth.[38,39] Chlorhexidine is effective as an anti-plaque agent when used after the mouth has been professionally cleaned.[40] However, although chlorhexidine blocks the formation of plaque, it is largely ineffective against established plaque because it is a cationic molecule that interacts strongly with proteins and therefore binds avidly to the surface layers of plaque but penetrates poorly.[41] Chlorhexidine therefore

has little activity against established plaque. In a study in which subjects brushed with a toothpaste containing 1% chlorhexidine for 6 months, significant reductions were found in plaque and gingival indices,[42] and in total plaque bacterial counts, but there was no effect on the composition of the plaque.[43] This exemplifies the resilience of the oral microbiota: specifically, a combination of brushing and the use of a relatively high concentration of the gold-standard anti-plaque agent continuously for 6 months did not affect the structure of the bacterial community in plaque. This study also reported a significant decrease in mean susceptibility of oral bacteria to chlorhexidine, but at a level not thought to be biologically significant (minimal inhibitory concentration: 2.68 mg/L [baseline] vs 3.19 mg/L [24 weeks]). Accordingly, there was no evidence that selection for, and replacement by, resistant organisms had occurred.

## 5 | SURVIVAL UNDER ADVERSE CONDITIONS

As discussed above, between human meals, bacteria live on the primary sources of nutrition available to them, namely saliva and gingival crevicular fluid. Growth rates on these substrates are slow. In the rapid phase of plaque formation of firmly attached organisms on a previously cleaned surface, doubling times of 3-4 h have been observed,[44] while doubling times of 8-12 h are seen in mature plaque.[45] By contrast, a *Pseudomonas* culture in complex medium may double every 15 minutes. In addition, oral bacteria may face other nutritional hardships—they may be deprived of nutrients by virtue of being in the center of a biofilm or they may be trapped in a root canal or under a restoration. It was once thought that all infected dentine should be removed from a caries-affected tooth before placing a restoration. It has been demonstrated conclusively, however, that sealing a lesion to prevent access of nutrients from the mouth leads to a good clinical outcome[46] and reduces the chance of pulp exposure during excavation of the lesion.[47] Interestingly, the bacteria that have been sealed in the lesion survive and have been shown to be viable after 5 months.[48] It has been shown that under such circumstances, bacteria can enter a dormant state in which they shut down most metabolic processes but can be resuscitated months or years later.[116] For this reason, common concepts of viability and vitality have little meaning and it has been shown that commercially available live/dead stains which purport to detect intact cell membranes should not be used to study oral mixed-species biofilms.[49] Every species may react differently with such stains, and bacteria in a dormant state may exhibit leaky membranes but still be capable of revival.

## 6 | DENTAL PLAQUE-ASSOCIATED ORAL DISEASE AND RESILIENCE

The association between diet and dental caries has been discussed above, specifically that excessive production of acid by oral bacteria degrades the buffering capacity of saliva, leading to lowered oral pH, a breakdown in resilience, and emergence of a dominant aciduric microbiota. The transition between health and disease in periodontal disease will be discussed in Chapter 10 and elsewhere in this volume of *Periodontology 2000*. The aspect most relevant to resilience of oral bacteria is that uninterrupted plaque formation leads to a change in the composition of plaque, with increased levels of gram-negative bacteria and anaerobes.[50] Endotoxins from gram-negative bacteria and other bacterial products irritate the gingivae and cause gingivitis.[51] In susceptible individuals, the disease state progresses to periodontitis, which is characterized by the formation of pockets between the teeth and gingivae that become heavily colonized by anaerobic bacteria. This provokes further inflammation to which the host responds, leading to a chronic lesion that, if left untreated, will result in tooth loss. Whether bacteria play a primary role in the initiation of periodontitis remains controversial[52] but there is good evidence that certain bacteria, such as *P. gingivalis* can subvert the host response to the detriment of periodontal health.[53] The periodontal pocket microbiota has been termed a dysbiosis – an altered normal microbiota. There is a conceptual problem with this view because the pocket microbiota only exists because of the disease (ie there is no "normal" healthy periodontal pocket bacterial community). It is clear, however, that at the level of the host ecosystem, periodontitis represents a deviation from the healthy norm and thus could be regarded as a loss of resilience.[4]

## 7 | ANTI-ADHERENCE PLAQUE-CONTROL STRATEGIES

Dental plaque forms in a structured way: first of all, bacteria bind to a pellicle-coated tooth surface (this binding is restricted to only a minority of species—the primary plaque-formers); then, other species (the secondary plaque-formers) attach to the developing biofilm by coaggregation interactions. Coaggregation studies have shown that *F. nucleatum* can bind to a wide range of other bacterial species and has therefore been thought to play a key bridging role in linking primary and secondary plaque-formers to create a cohesive and stable plaque structure.[75] Interestingly, however, direct microscopic examination of developing plaque found that *F nucleatum* had only limited physical interactions with other genera, while *Corynebacterium* species appeared to be an important scaffold.[54]

The importance of the initial adherence stage has led investigators to devise strategies for blocking bacterial adhesion as a plaque-control measure. For example, a graft copolymer, M239,144, was developed to block the hydrophobicity-mediated adhesion of *Streptococcus* species, which are important early plaque-forming organisms.[55] In in-vitro tests, M239,144 was extremely effective, reducing adhesion of reference strains of oral streptococci by up to 96%.[56,57] In a clinical trial, however, M239,144 showed no significant difference from water for plaque inhibition.[58] As discussed above, the functional redundancy of the oral microbiome is an important factor in its resilience. It is possible to block specific bacterial

adhesion mechanisms but the community, as a whole, has a wide variety of alternative adhesive strategies that enable it to circumvent such approaches. For example, streptococci alone have a number of cell-wall anchored adhesin proteins that mediate colonization and typically include domain repeats, which confer functional complexity via epitope variation, and thus redundancy.[59] Adhesins important in colonization of oral streptococci include Antigen I/II, the fibrillar adhesin CshA, serine-rich repeat proteins, and glycosyl transferases.[60]

## 8 | PREBIOTICS AND RESILIENCE

Oral bacteria play an important role in the maintenance of cardiovascular health via the reduction of dietary nitrate. When food rich in nitrate, such as leafy green vegetables and beetroot, is eaten, the nitrate is absorbed from the stomach into the bloodstream and then returns to the mouth after being concentrated by the salivary glands, a system known as the enterosalivary circuit.[61] Oral bacteria reduce nitrate to nitrite, which is converted in the body to nitric oxide. Nitric oxide has potent effects on blood vessels, making them more pliant, with the effect overall of lowering blood pressure. Dietary supplementation with nitrate has been shown to have significant blood pressure-lowering effects, of a magnitude similar to that of antihypertensive drugs.[62] Interestingly, the oral microbiota of individuals consuming nitrate-supplemented diets was altered and the proportions of nitrate-reducing bacteria, including *Neisseria* and *Rothia* species, were increased.[63] The enterosalivary circuit then, by supplying the oral microbiota with nitrate for extended periods, appears to mediate an exception to the rule that the oral bacteria are not affected by the human diet. Because *Neisseria* and *Rothia* are obligate aerobes and the anaerobe/aerobe ratio of plaque is correlated with gingival health, there is some interest in the possible use of nitrate as a prebiotic to modify the plaque microbiota in a beneficial way.

Sugar alcohols have been used as prebiotics because of their ability to block acid production by saccharolytic bacteria and thus reduce the risk of caries. Xylitol is the sugar alcohol most commonly used in this respect, and is incorporated into chewing gum and other topical delivery vehicles.[64] Studies investigating the effects of xylitol on the oral microbiota have been focused on caries-associated bacterial species and have generally shown reduced levels of such bacteria after xylitol use.[65] Use of chewing gum containing xylitol had no effect on the composition of the salivary microbiota, however,[66] and incorporation of maltitol, a related sugar alcohol, into a chewing gum had no effect on the composition of dental plaque after 2 weeks of use.[67]

## 9 | PROBIOTICS AND RESILIENCE

Probiotics are live microorganisms that are administered for their benefits on gut health. There is some evidence that they can reduce inflammation and strengthen the mucosal barrier.[68] The probiotics used are health-associated gut species and are primarily *Lactobacillus* and *Bifidobacterium* species. A number of these have been "rebadged" for oral use. Lactobacilli and bifidobacteria are, of course, associated with dental caries, so their administration to the mouth might not be advisable, particularly in individuals with high dietary sucrose intake.[69] In practice, however, adding extra bacteria to the oral ecosystem may have only a minimal effect because any selection of aciduric and acidogenic bacteria may have already occurred. Attempts have been made to modify the oral bacterial community using probiotic approaches, such as replacing the caries-associated organism, *Streptococcus mutans*, with *Streptococcus sanguinis*, but these have been unsuccessful because there appears to be a limited window of infectivity for *S. sanguinis*.[70] It appears that the mouth reaches a resilient steady state whereby oral surfaces are saturated with the resident microbiota, which physically block the attachment of external bacteria, and where, given the nutrient limitation, a full metabolic repertoire of obtaining nutrients from saliva and gingival crevicular fluid has been established, making it difficult for new organisms to become established. An alternative approach is to use attenuated *S. mutans* strains to occupy that species' niche,[71] and thus improve the potential for colonization with the modified strain.

A number of studies have investigated the potential for probiotics to prevent/treat dental caries and periodontal disease; mixed results were obtained, and overall this approach appears to be more promising for gingivitis than for caries (reviewed by Gruner et al[72]). Microbial surrogates are commonly used to assess efficacy and have primarily been bacterial species previously associated with the respective diseases. Rather fewer have looked at the effect of administration of probiotics on the composition of the oral bacterial community. Use of lozenges containing 2 strains of *Lactobacillus reuteri* resulted in a significant shift in composition of the oral bacterial community after 12 weeks: increased proportions of some species, including mitis-group streptococci, *Campylobacter concisus*, and *Granulicatella adiacens*, were observed, whereas the relative abundance of others, including *S. mutans*, *Fusobacterium* species, and *Prevotella maculosa*, was reduced.[73] This effect was reversed 1 month after the cessation of treatment. Increased diversity of salivary bacteria was seen after treatment with a mixed probiotic,[74] whereas no effect on the composition of the oral bacterial community was seen in studies evaluating different combinations of *Lactobacillus* strains, alone or with bifidobacteria.[75,76]

An alternative strategy would be to use health-associated oral bacteria as probiotics. One candidate with potential for use as a probiotic is *Streptococcus salivarius* strain K12: this organism has been shown to be antagonistic to Group A streptococci, which cause pharyngitis, and to anaerobes associated with oral malodor.[77,78] A systematic review of the use of *S. salivarius* K12 as a probiotic to prevent Group A streptococcus infection identified 4 studies, but all were considered to be of poor quality because of risk of bias.[79] The results of the studies were equivocal, with some showing a reduction in the number of episodes of pharyngitis and others showing no difference. Further studies are clearly required but, on the evidence available thus far, administration of *S. salivarius* K12 as a probiotic does not dramatically increase the resilience of the oropharyngeal

microbiota to acute infection. Administration of *S. salivarius* K12 after 3 days of treatment with a chlorhexidine mouthrinse has been shown to reduce the level of volatile sulfur compounds compared with controls.[80] *Lactobacillus*-based probiotics have also been reported to reduce the level of volatile sulfur compounds, and thus the organoleptic scores, in subjects with malodor,[81,82] although it was interesting that 1 study investigating the effect of incorporation of *L. reuteri* strains in chewing gum found a significant effect on organoleptic assessments, but not on the levels of volatile sulfur compounds, leading the authors to conclude that substances other than volatile sulfur compounds must contribute to malodor.[83]

There is clearly potential for the use of probiotics for the prevention, and possible treatment, of oral disease by reversing dysbiosis. Equally clear is the scale of the challenge of successfully and beneficially modifying a complex and naturally resilient microbiota.

## 10 | ROLE OF SALIVA IN RESILIENCE

One of the most important factors affecting oral bacterial communities is the presence of saliva.[84] The role of saliva as a nutrient source has already been described. Saliva also keeps the mouth moist, thus preventing bacterial desiccation as well as delivering a range of elements of innate and acquired immunity which modulate the oral microbiome.[85] These elements include antimicrobial peptides, lysozyme, and antibodies (primarily IgA and IgG). Despite the presence of these antimicrobial factors, a diverse oral bacterial community flourishes, so that it might be best to consider the oral microbiome as that collection of organisms that can colonize and grow in their presence. It has been demonstrated that, in the guts of mammals, antimicrobial peptides select for the microorganisms found and contribute to host-bacteria homeostasis in each species.[86] There is some evidence that host genetics plays an important role in determining the composition of the oral microbiome. In a study of 485 dizygotic and monozygotic twins, the composition of the bacterial community was significantly related to a shared host genotype, and a number of highly heritable taxa were revealed, although the majority of the variation was associated with environmental factors.[87] Interestingly, the caries-associated species detected were not among the heritable taxa, suggesting that, at least in terms of the bacteria involved, caries arises solely as a result of the effects of environmental, not genetic, factors. The basis for genetic control of bacterial composition would be the individual's profile of antimicrobial peptides and other immune factors.

Saliva includes a number of buffering systems, including those based on phosphate and bicarbonate that maintain an intraoral pH of around neutrality. This provides a stable environment for oral bacteria in the absence of perturbing external factors. If there is repeated acidification following excessive and/or over-frequent intake of fermentable carbohydrates, the buffering capacity of saliva is eroded and falls, leading to selection of aciduric bacteria, such as *S. mutans*, *Propionibacterium acidifaciens*, *Scardovia wiggsiae*, bifidobacteria and lactobacilli.[88-91] This loss of stability is reversible if dietary habits are improved leading to the restoration of the buffering capacity of saliva and the reestablishment of a microbiome associated with oral health.

## 11 | EFFECT OF DRY MOUTH ON RESILIENCE

Saliva, as described above, plays a major role in the maintenance of health-associated oral bacterial communities. Significantly reduced salivary flow, or xerostomia, can occur from conditions such as Sjogren's syndrome (which affects the salivary glands), as a side-effect of radiotherapy, or can be a common side effect of drug treatment.[92] It is thought that reduced salivary flow is the primary factor responsible for altering the composition of the bacterial community, and this has been demonstrated for subjects with primary Sjogrens's syndrome in whom salivary flow explained 90% of the variation seen between samples, whereas only 5% of variation could be assigned to disease status.[93] A key component of the bacterial changes seen in dry mouth is colonization by non-oral bacteria, such as coliforms and *Staphylococcus aureus*; in addition, a marked increase in the carriage rate of *Candida* species and in actual *Candida* infections is observed.[94] Colonization by non-oral bacteria probably occurs as a result of the loss of delivery of immune function, which would normally be mediated by saliva. Despite this, the few community profiling studies that have been performed comparing the bacterial composition of oral communities in subjects with hyposalivation with controls have shown no,[95] or only relatively minor, differences and some contradictory findings. For example, the proportions of streptococci in the tongue microbiota of patients with Sjogren's syndrome were found to be raised in 2 studies[96,97] and reduced in the salivary microbiota of another.[93] This disparity in findings may reflect the fact that standard profiling studies do not yield quantitative data and the primary effect of reduced salivary flow may well be microbial overgrowth. The use of improved methodology in tandem with bacterial and fungal culture studies is likely to show that dry mouth is one of the major perturbers of oral microbiota resilience.

## 12 | EFFECT OF NONORAL DISEASES ON ORAL MICROBIOTA RESILIENCE

There has been substantial interest in determining the effect of nonoral diseases, particularly those with systemic impact, on the oral microbiome. The results of such studies can be difficult to interpret, however. Statistical testing of microbial communities for associations involves a large number of individual tests, and appropriate corrections for multiple comparisons should be applied. In addition, the typical distribution of a human microbial population is one with a strong positive skew in which many of the taxa detected are found only rarely. When nonparametric ranking tests are used, a significant difference will be found between 2 groups when a taxon is found on a single occasion only in 1 of the groups.

For this reason, it is recommended that a minimum threshold either for prevalence (eg, a taxon should be found in more than 25% of samples) or for incidence (where a taxon should be present at a relative abundance of 1% or higher), should be applied, to ensure biological significance.

Acharaya et al[98] have reviewed the effects of nonoral disease on the salivary microbiome. A variety of effects were reported, which were often inconsistent between studies. Defects in immune function, such as those present in autoimmune diseases and immunodeficiency, frequently led to colonization of the oral cavity by nonoral bacteria, such as members of the *Enterobacteriaceae*, presumably because of the loss of immune control of the composition of the bacterial community discussed above.

Individuals with diabetes have significantly raised levels of glucose in blood, tissues, and (of particular importance to periodontitis) gingival crevicular fluid.[99] It might be predicted that a continuous supply of the most basic, simple sugar would provide a readily available nutrient source for oral bacteria and that total salivary bacterial counts would be increased. In fact, the converse has been shown to be true, with an inverse relationship between total salivary counts and salivary glucose levels.[100] The putative explanation for this is that when salivary glucose is high, saccharolytic bacteria produce acid, which lowers the oral pH and inhibits the growth of those bacteria that prefer a more alkaline environment. It has been previously observed that salivary pH is lowered in individuals with diabetes.[101]

Diabetes is associated with increased risk of caries[102] and periodontitis.[103] The nature of the relationship of diabetes with caries is self-evident and results from acidification of the mouth by bacteria because of raised salivary glucose levels. In both type I and type II diabetes, there is heightened systemic inflammation and this appears to exacerbate the inappropriate host response to bacterial challenge seen in periodontitis.[104] The relationship between periodontitis and diabetes appears to be bidirectional in that it has been shown that periodontal treatment improves diabetic control, leading to clinically significant reductions in the level of glycated hemoglobin.[105]

The consensus report of the Joint European Federation of Periodontology and Americal Academy of Periodontology Workshop on Periodontitis and Systemic Diseases states that there is inconclusive evidence that diabetes affects the composition of the periodontal microbiota.[106] Notwithstanding, some changes in the oral bacteria have been reported in individuals with diabetes. For example, the levels of saccharolytic bacteria, such as streptococci and lactobacilli, have been found to be raised,[107] while reduced levels of members of the phylum Actinobacteria have been observed.[108,109] Most diabetic individuals are presumably receiving treatment for their diabetes, which will reduce blood glucose levels. In order to determine the effect of uncontrolled hyperglycemia on the oral microbiome, it would be necessary to study individuals at the time of diagnosis. Indeed, significant clustering has been observed in groups of prediabetic and diabetic individuals with raised and severely raised levels of glycated hemoglobin.[110] Increased proportions of *Lactobacillus*, *Corynebacterium*, and *Pseudomonas* species were found in diabetic subjects, together with decreased proportions of *Treponema*, *Porphyromonas*, *Prevotella*, and *Parvimonas*.

Acute viral respiratory infections might be expected to modify the oral microbiome because of the large increase in secretions passing through the nose and mouth and damage to mucosal surfaces of the oropharynx caused by the causative virus. However, a study of 43 individuals experimentally infected with an influenza A strain and who developed proven infections, showed no changes in the composition of their pharyngeal bacterial communities, and no infections with secondary bacterial pathogens were detected.[111]

Hospitalization itself has been shown to have a significant effect on the composition of the gut microbiota.[112] The oral microbiome, by contrast, is resilient to this effect. Samples collected before, and 72 h after, hospital admission showed no differences in alpha- or beta-diversity comparisons.[113] This finding was confirmed in a study of frail older individuals admitted to hospital, for whom no change in oral bacterial community composition was found after admission.[114]

## 13 | CONCLUSIONS

The evidence presented in this review shows that the oral microbiome is undoubtedly naturally resilient. Furthermore, some principles can be established which explain this resilience and allow the prediction of which external factors might negatively affect this resistance. The bacteria found in the mouth appear to be selected by the actions of the host immune system. When this is disrupted, either by immunodeficiency or by reduced delivery of immune factors through a reduced volume of saliva, colonization with non-oral bacteria occurs. Oral bacteria normally use salivary glycoproteins, rather than food from the diet, for nutrition because food is swallowed quickly and washed away by salivary flow. As oral bacteria liberate simple sugars from the glycoproteins and possess mechanisms allowing the rapid uptake of these sugars, excess dietary sugar does affect their metabolism. The consequent overproduction of acid can also alter the environment by reducing the pH of saliva, thus promoting the growth of aciduric bacteria. Nitrate can be found for extended periods of time in the mouth because of the existence of the enterosalivary circuit, which makes nitrate available to oral bacteria and this can affect the composition of the bacterial community in the oral cavity. In periodontal disease, poor oral hygiene leads to excessive plaque formation, which causes connective tissue attachment loss between the gingivae and teeth and the subsequent formation of a periodontal pocket. This is a new anatomical structure which becomes heavily colonized with anaerobic bacteria, some of which subvert the host response to cause a chronic nonhealing lesion. This combination of host and external factors can be viewed as a loss of health-associated resilience. Nonoral diseases can influence the composition of the oral microbiome either by interfering with the immune system or, in the case of diabetes, by causing raised levels of glucose.

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